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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/117810	Schutzetal.
Examiner	**Group Art Unit**
Lu, Frank	1634

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 5-24-02.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 5-9 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☐ Claim(s)____ is/are allowed.

☒ Claim(s) 5-9 is/are rejected.

☐ Claim(s)____ is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s).____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☒ Other Detailed Action

Office Action Summary

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 24, 2002 has been entered. The claims pending in this application are claims 5-9. Rejection and /or objection not reiterated from the previous office action are hereby withdrawn. The following rejections are based on amendment.

Claim Objections

2. Claim 5 is objected to because of the following informalities: " western blow" should be "western blot".

3. Claims 8 and 9 are objected to as being in improper dependent claim because claims 8 and 9 (kit claim) do not include every limitation of claim 1 from which they depend (do not need method steps) since claim 1 is directed to a method. See Infringement test in MPEP § 608.01(n).

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 5-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 6-9 are dependent on claim 5.

6. Claim 5 is rejected as vague and indefinite in view of the phrase "wherein if CREM is not expressed or expressed only to a reduced extent and not expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins are not expressed either or expressed only to a reduced extent, there will be unbalanced spermatogenesis resulting in non-functioning spermia" because it is unclear what it intended. For example, the word "if" in this phrase appears to give two possible forms of CREM in a male animal: (1) CREM that "is not expressed or expressed only to a reduced extent and not expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins are either not expressed or expressed only to a reduced extent, there will be unbalanced spermatogenesis resulting in non-functioning spermia" as recited in the claim; and (2) CREM that is expressed or expressed only to an increased extent and expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins are either expressed or expressed to an increased extent, there will not be unbalanced spermatogenesis not resulting in non-functioning spermia that is not recited in the claim. However, it is unclear why the claim only describes the first possible form of CREM. Please clarify.

7. Claim 5 are rejected as vague and indefinite in view of step (a) because it is unclear what it intended. Does this step mean that detecting the presence of CREM and/or CREM-dependent DNA in samples taken from said male animal's testis by amplifying DNA coding for CREM

and/or CREM-dependent proteins using primers specific for CREM and/or CREM-dependent protein in the presence of necessary reagents for amplification or does this step mean something else? Please clarify.

8. Claim 5 are rejected as vague and indefinite in view of step (b) because it is unclear what it intended. Does this step mean that detecting the presence of CREM and/or CREM-dependent proteins in samples taken from said male animal's testis by conducting a western blot analysis using antibodies against CREM and/or CREM-dependent protein in the presence of necessary reagents for western blot or does this step mean something else? Please clarify.

9. Claim 5 are rejected as vague and indefinite in view of step (c) because it is unclear what it intended. Does this step mean that detecting the presence of CREM and/or CREM-dependent mRNAs in samples taken from said male animal's testis by conducting a northern blot analysis in the presence of necessary reagents for northern blot or does this step mean something else? Please clarify.

Claim Rejections - 35 U.S.C. § 102/103

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 5 and 7 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Delmas *et al.,* (Mol. Endocrinol. 7, 1502-1514, November 1993).

Note that this rejection was made in view of the ambiguity of claim 5 and basing on the interpretation of the phrase "wherein if CREM is not expressed or expressed only to a reduced extent and not expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins are not expressed either or expressed only to a reduced extent, there will be unbalanced spermatogenesis resulting in non-functioning spermia" (see above). In this rejection, the examiner considered that CREM was expressed or expressed only to an increased extent and expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins were either expressed or expressed to an increased extent and there would not be unbalanced

spermatogenesis not resulting in non-functioning spermia (see the second forms of CREM in the rejection under 35 U.S. C § 112).

Delmas *et al.*, teach induction of cAMP-responsive element modulator (CREM) activator proteins in spermatids and their down-stream targets. They showed that CREM tau was efficiently phosphorylated at a serine residue at position 117 by the protein kinase-A endogenous to germ cells. This indicated that CREM tau constitutes a natural target of the adenylyl cyclase pathway during spermatogenesis. The phosphorylated CREM tau became a powerful activator. The rise in CREM tau protein coincided with the transcriptional activation of several genes such as the male germ cell-specific RT7 as recited in claim 7. The RT7 promoter was shown to be cAMP inducible and activated by CREM tau in transfection assays (page 1502, abstract). Using Western and Northern analysis as recited in claim 5, they further showed that R7 RNA appeared on exactly the same day as CREM proteins were first produced. As a control, the same Northern blot was hybridized with an actin probe to show that comparable amounts of RNA were loaded in each lane (as a standard reagent). These experiments revealed a good correlation between CREM protein synthesis and RT7 transcription activation (first paragraph of left column in page 1509 and Figure 6). Note that: (1) although Delmas *et al.*, did not directly show to puncture a male animal's testis as recited in claim 5, in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference of Delmas *et al.*, since "testes from the same mice at different ages were used to prepare protein extract and RNA" (see page 1509, left column) suggested that Delmas *et al.*, collected testes by multiple biopsies of the same mouse's testis; and (2) although Delmas *et al.*, did not directly show monitoring

spermatogenesis using CREM and /or CREM-dependent protein as described in claim 5, in the absence of convincing evidence to the contrary the claimed invention, this limitations was considered as inherent to the reference taught by Delmas *et al.,* since it was well known that CREM had a pivotal role during the developmental process of male germ cells (ie.,spermatogenesis) (see a review by Delmas *et al.,* Mol. Cell. Endocrinology, 100, 121-124, 1994).

Response to Arguments

In page 5 of applicant's remarks, applicant argued that : (1) "Delmas et al do not disclose or suggest the correlation between deficient CREM/CREM-dependent protein and unbalanced spermatogenesis and ultimately non-functioning spermia."; and (2) "Delmas et al could not possibly disclose or suggest detecting and monitoring the presence of CREM and/or CREM-dependent proteins as a means of investigating and monitoring spermatogenesis in a male animal."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, from the examiner's interpretation of the phrase " wherein if CREM is not expressed or expressed only to a reduced extent and not expressed in a phosphorylated form, respectively, so that CREM-dependent-dependent proteins are not expressed either or expressed only to a reduced extent, there will be unbalanced spermatogenesis resulting in non-functioning spermia" (see above), the examiner did not considered that claim 5 included the correlation between deficient CREM/CREM-dependent protein and unbalanced spermatogenesis and ultimately non-functioning spermia since it was obvious that the word "if "

in this phrase suggested two possible forms of CREM (see above rejection under 35 U.S. C § 102/103). Second, since the reference showed the detection of the expression of CREM and/or CREM-dependent protein (i.e., R7) and it was known that spermatogenesis included before and after meiosis of germ cells (see a review by Delmas *et al.,* Mol. Cell. Endocrinology, 100, 121-124, 1994), the examiner considered that Delmas *et al.*, did taught the process of investigating spermatogenesis. Third, although Delmas *et al.,* did not directly show monitoring spermatogenesis using CREM and /or CREM-dependent protein as described in claim 5, in the absence of convincing evidence to the contrary the claimed invention, this limitations was considered to be inherent to the reference taught by Delmas *et al.,* since it was known that CREM had the pivotal role during the developmental process of male germ cells (see a review by Delmas *et al.,* Mol. Cell. Endocrinology, 100, 121-124, 1994).

13. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delmas *et al.,* (1993) as applied to claims 5 and 7 above, and further in view of Bockers *et al.*, (Cell Tissue Res. 278, 595-600, 1994).

The teaching of Delmas *et al.,* have been summarized previously, *supra.*

Delmas *et al.,* do not disclose to investigate and monitor spermatogenesis in a male human as recited in claim 6.

Bockers *et al.*, teach the localization of FSH immunoreactivity and hormone receptor mRNA in testicular tissue of infertile man using testicular biopsy (see abstract in page 595, right column in page 595, and left column in page 596).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have investigated and monitored spermatogenesis using the method of Delmas *et al.*, in a male human in view of the reference of Bockers *et al.*. One having ordinary skill in the art would have been motivated to use method of Delmas *et al.*, in a male human because: (1) the use of human as an experimental model not only could further confirm the experimental results obtained from an animal model but also directly study the effects of CREM during the developmental process of human germ cells and compare the experimental results from different animal models so that one having ordinary skill in the art could develop a potential animal model for studying idiopathic infertility in man; and (2) the application of a known method in one animal model (ie., male human) instead of another animal model (ie., male mouse) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

14. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delmas *et al.,* (1993) as applied to claims 5 and 7 above, and further in view of Stratagene Catalog (1988, page 39).

The teachings Delmas *et al.,* of have been summarized previously, *supra.* They also showed that, in cotransfection experiments, CREMτ expression vector and a reporter chloramphenicol acetyl transferase (CAT) vector containing the RT7 promoter cAMP-responsive element (CRE) were cotransfected into human choriocarcinoma JEG-3 cells. Coexpression of CREMτ enhanced activation of the RT7 CRE by cAMP and suggested that the RT7 CRE was functional and potentially represented a cellular target of CREM transregulatory function (second paragraph of left column in page 1509 and Figure 7 in page 1510). The expression vectors could be considered as carriers or conventional vehicles as recited in (e) of claim 8. Note that CREM-specific antibodies as recited in (b) of claim 5 blocked RT7 *in vitro* transcription (see page 1502, abstract), and RT7 and actin probes were considered as standards and detection reagents respectively in the Northern Blot as recited in (d) of claim 8 (see Figure 6).

Delmas *et al.,* teach all limitations in claims 8 and 9 except a kit.

The Stratagene catalog (page 39) discloses the general concept of kits for performing gene characterization assays and discloses the advantages of kits. The kit format is utilized not only assemble a variety of different reagents together but ensure the quality and compatibility of the reagents.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have organized the

components taught by Delmas *et al et al.*, into a kit because the method for investigating and monitoring a process of spermatogenesis was conventional at that time the inventions were made and the kit format was utilized not only to assemble a variety of different reagents together but ensured the quality and compatibility of the reagents. The Stratagene Catalog (1988) would have motivated and suggested the assemblage of reagent (s) of biotechnology methods into a kit in order to obtain the above discussed advantages, thus resulting in instant kit described in claims 8 and 9. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to assemble reagents of Delmas *et al.*, into a kit because the kit could provide a convenient, efficient, economical way to practice the method of Delmas *et al.*.

Conclusion

15. No claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
July 12, 2002